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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,864	05/14/2001	Lars Eyde Theill	A-686B	9916

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U.S. Patent Operations/ TJG
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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	15

DATE MAILED: 02/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/854,864	Applicant(s) THEILL ET AL.	
	Examiner Maher M. Haddad	Art Unit 1644	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *3,4,22-24 and 38-45* is/are pending in the application.

4a) Of the above claim(s) *39-41 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-4,22-24, 38 and 42-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 1/16/03 (Paper No. 13), is acknowledged.

Claims 3-4, 22-24 and 38-45 are pending.

2. Newly submitted claims 39-41 and 45 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: since Applicants elected SEQ ID NO: 13 as the species for the search purposes and the Examiner extended the search to include SEQ ID NO:15, then the non-elected SEQ ID NOS: 6, 16 and 7, and anti-APRIL antibody claimed in claims 39-41 and 45 are not originally searched and examined.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 39-41 and 45 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

3. Claims 39-41 and 45 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 3-4, 22-24, 38, and 42-44 are under consideration in the instant application as they read on a method of inhibiting TACI activity, BCMA activity or both in mammal comprises adininstering a specific binding partner for APRIL and further comprising adminitering a specific binding partner for AGP-3 as they read on SEQ ID NO:13 and SEQ ID NO:15.

5. Claims 43-44 are objected to because they are dependent on a non-elected claims 39-41.

6. The following new grounds of rejections are necessitated by the amendment filed on 1/16/03, paper No. 13.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 22-23, 38 and 42-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The term "multimer" in claim 22, line 8 is indefinite, it is unclear how the specific binding partners of APRIL and AGP-3 would multimerize in the absents of Fc domain.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 3-4, 22-24, 38 and 42-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting TACI activity, BCMA activity, or both in a mammal, which comprises administering the TACI/BCMA extracellular consensus sequence (SEQ ID NO:13), the extracellular region of TACI (SEQ ID NO:15), the extracellular region of BCMA (SEQ ID NO:6), the consensus region of TACI (SEQ ID NO: 16) and the consensus region of BCMA (SEQ ID NO: 7) and an anti-APRIL antibody, does not reasonably provide enablement for a method for inhibiting TACI activity, BCMA activity, or both in a mammal, which comprises administering any binding partner for APRIL in claim 3; said method further comprising administering any binding partner for AGP-3 in claim 4; wherein the specific binding partner **comprises** any sequence recited in claim 22, where in the specific binding partner **comprises** the extracellular region of TACI (SEQ ID NO:15) in claim 38, Wherein the specific binding partner **comprises** the TACI/BCMA extracellular consensus sequence (SEQ ID NON:13) in claim 42. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims essentially for the same reasons set forth in the previous Office Action, paper No. 11, mailed 7/16/02.

Applicant's arguments, filed 1/16/03 (Paper No. 13), have been fully considered, but have not been found convincing.

Applicant argues that the specification provided specific working examples of binding partners of APRIL that include more than just the sequences and Applicant further directed the Examiner attention to page 64 and 71 lines 6-15, where an anti-APRIL antibody is described and used in a biological assay. Applicant further argues that the specification provides extensive teaching that is prophetic on how to make polypeptides, antibodies, peptides and muteins that would function as binding partners of APRIL or AGP-3. Applicant further argues that the sweeping language of the rejection in the Office Action appears to violate the principle that a single working example in the specification for claimed invention is enough to preclude a rejection which states that noting is enabled. Applicant argues with regard to the undue experimentation that the specification teaches how one can make various modifications to the polypeptides to develop alternative sequences that function as a binding partner to APRIL or further AGP-3 and are capable of inhibiting TACI. Applicant further argues that the changes can be made by standard mutagenesis, and the activity of the polypeptides can be tested in the assays taught by the specification. Applicant argues regarding different structures would be expected to have differences in activity that the experimentation required to practice the invention is not undue because the generation, production and screening of variant binding partners of APRIL and/or AGP-3 is routine and the activity of the molecules used in the methods can be routinely measured by standard assays.

The term "comprises" in claims 22, 38, and 42 is open-ended, it expand the amino acid sequence of SEQ ID NOS: 6-7, 13 and 15-16 to include additional non disclosed amino acids outside of the "the TACI/BCMA extracellular consensus sequence" and "the extracellular region of TACI".

It is noted that Applicant's disclosure regarding the antibody #c19 activity that it inhibits generation of anti-Pneumovacs specific antibodies in vivo appears to be at odds with what someone wants to achieve. Pneumovac vaccine is given for immunization against pneumococcal disease caused by those pneumococcal types, wherein protective antibody levels develop following vaccination. Therefore, it is unclear why would someone wants to inhibit the generation of the protective anti-Pneumovacs specific antibodies.

Regarding the sweeping language of the rejection in the Office Action, Examiner notes that the previous Office Action mailed on 7/16/02, indicated the that the specification is being enabled for a method of inhibiting TACI activity, BCMA activity, or both in a mammal, which comprises administering the TACI/BCMA extracellular consensus sequence (SEQ ID NO:13), the extracellular region of TACI (SEQ ID NO:15), the extracellular region of BCMA (SEQ ID NO:6), the consensus region of TACI (SEQ ID NO: 16) and the consensus region of BCMA (SEQ ID NO: 7). However, the specification fails to provide any guidance as to how to make and how to use any "binding partner for APRIL" or any "binding partner for AGP-3" including any antibody, any polypeptide and any Fc-fusion.

Applicant is relying upon certain biological activities and the disclosure of SEQ ID NOS:13, 15, 6, 16 and 7 and the anti APRIL antibody species to support an entire genus. It is well known that minor structural differences among even structurally related compounds or compositions can result in substantially different biology, expression, and pharmacology of proteins. Therefore, structurally unrelated any "specific binding partner for APRIL" or any "specific binding partner for AGP-3" would be expected to have greater differences in their activities. Since the amino acid sequence of a polypeptide determines its structure and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality requires knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification) and detailed knowledge of the ways in which a polypeptide's structure relates to it's functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects of APRIL or AGP-3, and finally, what changes can be tolerated with respect thereto is complex and well outside the realm of routing experimentation.

The claims as written encompass a broad genus of polypeptides with an unlimited number of possibilities with regard to the length of the polypeptide sequence. Further, making changes up to mutagenesis in polypeptide sequences do not provide the resultant mutant polypeptide will

retain the same inhibitory activity as the unmutated polypeptide. One of ordinary skill in the art cannot envision all of the amino acid changes encompassed by the breadth of the claims and still inhibiting TACI and/or BCMA activity.

Consequently, without additional guidance in the specification, and the dearth of information in the art, for one of skill in the art to practice the invention as claimed, would require experimentation that is excessive and undue. The amount of guidance or direction needed to enable an invention is inversely related to the mount of knowledge in the state of the art as well as the predictability in the art (In re Fisher, 427 F.2d 833, 839, 166 USPQ 18,24 (CCPA 1970)).

11. Claims 3-4, 22-24, 38 and 42-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention essentially for the same reasons set forth in the previous Office Action, paper No. 11, mailed 7/16/02.

> Applicant is in possession of a method of inhibiting TACI activity, BCMA activity, or both in a mammal, which comprises administering TACI/BCMA extracellular consensus sequence (SEQ ID NO:13), the extracellular region of TACI (SEQ ID NO:15), the extracellular region of BCMA (SEQ ID NO:6), the consensus region of TACI (SEQ ID NO: 16) and the consensus region of BCMA (SEQ ID NO: 7) and an anti-APRIL antibody.

Applicant's arguments, filed 1/16/03 (Paper No. 13), have been fully considered, but have not been found persuasive.

Applicant argues that an adequate written description can be achieved by (1) a description of peptides and peptide fusion molecules including structures, muteins, and amino acid substitutions and (2) extensive working examples of the three different molecules.

However, the Examiner notes that the claimed invention which is drawn to a genus may be adequately described if there is a (1) sufficient description of a representative number of species, or (2) by disclosure of relevant, identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. To satisfy the disclosure of a "representative number of species" will depend on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. "Relevant, identifying characteristics" include structure or other physical and /or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus. (see Revised Guidelines for the Examination of Patent

Applications Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001).

In the instant case, however, there is no described or art-recognized correlation or relationship between the structure of the invention, the TACI/BCMA extracellular consensus sequence, the extracellular region of TACI, the extracellular region of BCMA, the consensus region of TACI and the consensus region of BCMA, the anti-APRIL antibody and their TACI and/or BCMA inhibitory function, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of a specific binding partner for APRIL, a specific binding partner for AGP-3 which retain the features essential to the instant invention.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

13. Claims 3-4, 22-23, 38 and 43 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,969,102, as is evidenced by Ware (J.Exp. Med 192:F35-F37, 2000) essentially for the same reasons set forth in the previous Office Action, paper No. 11, mailed 7/16/02.

Applicant's arguments, filed 1/16/03 (Paper No. 13), have been fully considered, but have not been found persuasive.

Applicant argues that the Federal Circuit has held that inherency requires that the missing descriptive matter is necessarily present in the thing taught in the art and that it would be so recognized by one of ordinary skill in the art. Applicant further argues that a thing may or may not be present, is not sufficient to show inherency. Applicant argues that the `102 patent suggests that the extracellular domain of TACI can be used to inhibit TACI activity, which is only prophetic and no actual experiments were conducted to demonstrate this inhibition. Furthermore, Applicant argues that the `102 patent does not teach that the extracellular domain needs to be multimerized as show by the specification and hence the non-multermerized extracellular domain of TACI would likely have had little inhibitory activity. Applicant argues that the `102 patent does not teach that the extracellular domain of TACI is a specific binding partner for APRIL, nor does it teach that administration of the extracellular domain of TACI will inhibit BCMA activity.

Contrary to the Applicant assertions, the `102 patent teaches methods of inhibiting TACI activity by various means such as the free N-terminal extracellular domain of TACI (claimed SEQ ID NO:15) and the expression of a non-functional extracellular domain lacking a signal transduction domain, e.g., GPI-linked N-terminal TACI (column 40, lines 45-57 in particular) in human or any animal (column 42, lines 7-13 in particular).

While the prior art disclosure is silent as to the "the extracellular region of TACI (SEQ ID NO:15) binds to APRIL and AGP-3" and the "specific binding partner is a multimer" per se; the method of treatment, patients and the product used in the method are the same as the claimed invention. Therefore, binding of the extracellular region of TACI (SEQ ID NO:15) to APRIL and AGP-3 and the "specific binding partner is a multimer" are considered an inherent property.

Further, as is evidenced by Ware, that BCMA and TACI bind APRIL and BAFF (AGP-3) with relatively high affinity. Ware concluded that direct intervention targeted at BAFF, APRIL or both is readily accomplished with the soluble decoys of TACI or BCMA. This could be the pharmaceutical version of the "two for the price of one" (page F37, left column, last paragraph in particular).

Applicant is reminded that under the principles of inherency, if a prior art method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art. When the prior art method is the same as a method described in the specification, it can be assumed the method will inherently perform the claimed process. See MPEP 2112.02.

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 22-24, 38 and 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,969,102, as is evidenced by Ware, in view of U.S. Patent No. 6,165,745 for the same reasons set forth in the previous Office Action, paper No. 11, mailed 7/16/02.

Applicant's arguments, filed 1/16/03 (Paper No. 13), have been fully considered, but have not been found persuasive.

Applicant argues that the `745 patent fails to teach that Fc fusions could be mad with TACI, BCMA, APRIL or AGP-3, their extracellular domains, or any fragment thereof, other than to generally provide a suggestion that half lives of any fusion molecule with Fc domains can have extended half lives. Applicant further argues that the `745 patent teaches that the Fc domain itself can bind to larg e numbers of immune cells bearing its receptor in a non-specific manner

hence the a TACI-Fc fusion, would cause Fc to interact with immune cells bearing Fc receptors and stimulate them.

Contrary to Applicant assertions, the combination of references do provide clear motivation and expectation of success in to link Fc domains to SEQ ID NO: 15 and use it in the methods of inhibiting TACI activity in a mammal because such chimeric have the advantage of prolonged half lives. Further it is noted that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In re Fine , 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones , 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Applicant is reminded that obviousness does not require absolute predictability but only the reasonable expectation of success. See In re Merck and Company Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988). MPEP 2143.02.

16. No claim allowed

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the

Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
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February 24, 2003

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